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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,020	08/21/2001	Sydney Brenner	55525-8055.US00	7541

22918 7590 10/19/2006

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EXAMINER	
STEELE, AMBER D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,020	BRENNER, SYDNEY	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 7 and 10 were amended in the amendment to the claims received on July 20, 2006.

Claims 1-10 are currently pending.

Claims 7-10 are currently under consideration.

Election/Restrictions

2. This application contains claims 1-6 drawn to an invention nonelected without traverse in the reply received on April 9, 2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objections

3. The objection to the drawings regarding Figure 2A (214); Figure 2B (126) and (236); Figure 2C (254) and (260); Figure 2D (269), (270), (271), and (272); Figure 3 (308); Figure 5A (556); and Figure 8B (864) is withdrawn due to the amendments to the specification and the drawings received on July 20, 2006.

Maintained Objection

Drawings

4. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: **Fig. 2B (234)**. Corrected drawing sheets in compliance with 37 CFR 1.121(d), **or amendment to the specification to add the reference character(s) in the description** in compliance with 37 CFR

1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Withdrawn Rejections

5. The rejections of claims 7-10 under 35 USC § 112, second paragraph are withdrawn due to the amendments to the claims received on July 20, 2006.

Maintained Rejections

6. Please note that the rejections have been modified to incorporate the claim amendments received on July 20, 2006 or to clarify terms. Regarding the two separate 35 USC § 112 written description rejections, the rejections have been combined in order to clarify the rejection based on applicant's arguments.

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

8. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

Claim 7 is drawn to a method of making a reference library comprising:

(A) digesting pooled nucleic acid with a restriction endonuclease,

(B) ligating an Exo III resistant linker with a 3' overhang to the fragment(s) of (A),

(C) digesting the product(s) of (B) with a restriction endonuclease different form the one in step (A) above,

(D) ligating an Exo III susceptible linker with a 5' overhang to the product(s) of (C),

(E) digesting the product of (D) with Exo III,

(F) denaturing the product of (E) and hybridizing,

(G) contacting the product(s) of (F) with a second member to enrich and form a reference population of restriction fragments containing a Exo III susceptible linker.

The invention as claimed encompasses all known nucleic acid fragments and/or reference libraries and all potential nucleic acid fragments and/or reference libraries since virtually any nucleic acid can be cleaved with at least one restriction endonuclease (e.g. present claim 7). In addition, the invention encompasses all known and unknown restriction endonucleases. The claimed invention states that a reference library is produced via various steps of digestion with various restriction endonucleases. The claimed invention does not include any structural information regarding the nucleic acid fragments that make up the reference library except that the starting nucleic acid and subsequent fragments contains restriction site(s). Moreover, Exo III

susceptible and Exo III resistant linkers are added to the nucleic acid fragments and no structural features of the linkers are provided except for the art-recognized structure that a blunt end or 5' overhang must be present for Exo III activity and a 3' overhang for Exo III resistance (e.g. must the linker contain an overlap for ligation to restriction endonucleases that leave an overhang after cleavage?; is it advantageous to digest the overhang and blunt end ligate the linker – although art recognized that blunt end ligation is more difficult than ligation of overhangs?; must only restriction endonucleases that leave an overhang be utilized due to the difficulty in blunt end ligation?, how does the method ensure that the proper orientation is maintained?, does the orientation of the nucleic acids matter?, etc.). In addition, the claimed invention does not include any structural information regarding how the first or second restriction endonuclease is chosen. Are a certain number of cuts (via a restriction endonuclease) advantageous? Is a certain fragment length advantageous (e.g. utilize rare sites over common sites or vise versa)? Should only restriction endonucleases that recognize "common" sequences be utilized? Should the linker be formulated so that it is resistant to the restriction endonucleases utilized? Should the first restriction endonuclease cleave a "common" sequence and the second restriction endonuclease cleave a less "common" sequence or vice versa? Wouldn't "common" sequences be different in different species? The scope of the claims include a vast number of sequences because the specification and claims do not place any limit on the number of components (e.g. nucleic acids) or the type of components (e.g. natural or unnatural nucleic acids). Therefore, Applicant is using an inadequately described "nucleic acid fragment" derived from cleavage of inadequately described "restriction endonucleases" (e.g. reagents utilized in the method) to inadequately describe the claimed method of making a "reference library". Consequently, there is no teaching

that would allow a person of skill in the art to determine *a priori* that the Applicant was in possession of the full scope of the claimed invention at the time of filing because there is no common structural attributes that can link together all of the claimed "nucleic acid fragments" and "restriction endonucleases" that make the "reference library" by the presently claimed method.

The Specification provides a "laundry list" (please refer to MPEP § 2163) of restriction endonucleases including Sau 3A, Taq I, Bst YI, Tsp 509I, Nla III, Msp I, Hin P1 I, Hha I, Aci I, Bsp 120I, Eco RI, Pac I, Bbs I, Bam HI, Dpn II, Pst I, Eco RV, Hind III, Bse RI, Bbv I, Xho I, Cla I, and Sap I (please refer to Figures 6-10; page 14, lines 10-19; page 35; page 37, line 12; and Examples 1-3). In addition, the specification teaches a Q, ssssN, M, ZavaW, SEQ ID No: 14, and SEQ ID No. 15 adaptors (please refer to page 51, lines 26-28; page 52, lines 1-6, page 53, lines 16-30). Furthermore, the specification teaches "reference libraries" of p0T2S and p1T2S plasmids derived from the pUC19 plasmid (see Example 1), genomic DNA isolated from white blood cells of diabetic and nondiabetic patients (see Example 2), and pUCSE plasmids derived from the pUC19 plasmid (see Example 3). Additionally, the Applicant asserted that the invention as claimed encompasses "any of a large number of known restriction endonucleases" and "thousands of linkers" in the response received on July 28, 2003 (see page 2, last paragraph). Moreover, there are over 200 commercially available restriction endonucleases each of which recognizes a unique sequence (see the New England Biolabs® website, for instance) and conservatively millions of linkers that could be engineered with blunt ends, 5' overhangs, or 3' overhangs comprising dsDNA, DNA-RNA hybrids, and combination double stranded (ds) and single stranded nucleic acids. Furthermore, the specification does not teach how the first or

second restriction endonucleases should be chosen. Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the entire scope of the invention as claimed since the structural limitation of the cleavage site for the restriction endonuclease(s) is not included in the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

Additionally, Cf. University of Rochester v G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer Inc., No. 03-1304, 2004 WL 260813 (Fed. Cir., Feb. 13, 2004) held that:

Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can

provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

While the general knowledge and level of skill in the art for utilizing restriction endonucleases to make nucleic acid fragments is high, this knowledge and level of skill does not supplement the omitted description because specific, not general, guidance is needed for the "reference library" being made by cleaving nucleic acid(s) with restriction endonucleases of the presently claimed method. Since the disclosure fails to describe the common attributes or characteristics that identify all of the members of the genus or even a substantial portion thereof, and because the genus is vast and highly variant (e.g. billions of fragments), the limited examples in the specification (please refer to Examples 1-3 in the Specification) are insufficient to teach the entire genus. The specification discloses only limited examples that are not representative of the claimed genus of a "reference library", "nucleic acid fragments", or "restriction endonulceases" (e.g. the reagents necessary to perform the presently claimed method and the subsequenct product of the presently claimed method); nor do the claims recite sufficient structural feature(s) which is(are) common to members of the genus sufficient to demonstrate possession of the genus. Moreover, in the examples provided in the specification specific restriction endonucleases were utilized to produce the above mentioned "reference libraries". If different restriction endonucleases were utilized to digest the starting material, a completely different "reference library" would be formed. Therefore, the teachings in the specification are general teachings relating without guidance as to the individual components of the product made by the presently claimed method. In addition, there are numerous "nucleic acid fragments", "restriction endonucleases", and/or "reference libraries" that could be employed in the invention

with little direction or guidance for one of skill in the art to practice the claimed invention. The expedient statements in the specification do not relate to an adequate disclosure or how to make and use the claimed invention. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to adequately describe the vast genus. Thus, Applicant does not appear to be in possession of the claimed genus.

Arguments and Response

9. Applicant's argument directed to the rejection under 35 USC § 112, first paragraph (written description), for present claims 7-10 have been fully considered but are not persuasive for the following reasons.

Applicant alleges that the written description rejection is based on the product and not on the presently claimed method.

Applicant's arguments are not convincing since two written description rejections were on record (e.g. one pertaining more specifically to the reagents utilized in the method and the intermediate and final product of the method and one pertaining more specifically to the method steps). In order to clarify the rejection for the applicant, the two previous written description rejections have been consolidated into one written description rejection. The present written description rejection is based on the scope of the method steps, the scope of the reagents utilized in the method steps, the scope of the intermediate products produced after each step of the method, and the scope of the ensuing product produced by the method as presently claimed. The entire scope of the vast genuses are not adequately described in the specification (e.g. adequate support for a representative group form each genus is not provided). Therefore, applicant is not in possession of the entire scope of the presently claimed method.

Claim Rejections - 35 USC § 102

10. Claim 7 is rejected under 35 U.S.C. 102(e) as being anticipated by Short et al. U.S. Patent 6,352,842 B1 (filed March 26, 1999).

Short et al. (see entire document) teach directed evolution utilizing restriction endonucleases and exonulcease III (please refer to the abstract). Short et al. teach methods of directed evolution including steps for digesting nucleic acids with various restriction enzymes or polynucleotide-acting enzymes and optionally repeating those steps (e.g. present claim 7 steps (A) and (C); please refer to column 5, lines 1-15, column 9, lines 49-65, column 16, lines 36-54, column 56, lines 23-67, columns 57-58, and column 59, lines 1-6), steps for producing Exo III resistant (3' overhang) and susceptible (5' overhang or blunt end) nucleic acids or linkers and ligation (e.g. present claim 7 steps (B) and (D); please refer to column 9, lines 66-67, column 10, lines 1-11, column 12, lines 4-16, and column 38), steps for digesting nucleic acids with Exo III (e.g. present claim 7 step (E); please refer to column 37, lines 9-67, column 38, and column 39, lines 1-35), and steps for denaturing and hybridizing nucleic acids (e.g. present claim 7 step (F); please refer to column 37, lines 10-22 and 55-67, and column 38, lines 1-7). In addition, Short et al. teaches that the products of the directed evolution methods can be bound and enriched for members of the nucleic acid population which hybridize or bind (e.g. present claim 7 step (G); please refer to column 40, lines 38-60). Furthermore, Short et al. states that any commercially available or non-commercially available polynucleotide endonucleases can be utilized in the directed evolution methods including the presently elected species of Sau3A I and Taq I as evidenced by Roberts and Macelis (please refer to column 56, lines 42-57 and Roberts and Macelis, REBASE – restriction enzymes and methylases, Nucleic Acids Research, 24(1): 223-

235, 1996). Therefore, one of skill in art would have anticipated the presently claimed invention in view of the teachings of Short et al.

Arguments and Response

11. Applicant's arguments directed to the rejection under 35 USC 102(e) as being anticipated by Short et al. for present claim 7 was considered but are not persuasive for the following reasons.

Applicant contends that every element of the claimed invention must be identically shown in a single reference and the Short et al. patent does not teach the method embodied by steps (a)-(g) of the applicant's claim (cites MPEP § 2131 and *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990)).

Applicant's arguments are not convincing since the teachings of Short et al. do anticipate the presently claimed method of the instant claims. It is the examiner's position that Short et al. teaches each and every limitation of the presently claimed method (please refer to the rejection above). In addition, it is unclear what limitation(s) the applicant contends is missing from the Short et al. reference since the applicant has failed to specifically point out the supposed shortcomings of Short et al. It is the examiner's position that Short et al. teaches methods comprising digesting nucleic acids with restriction enzymes, ligating linkers including Exo III resistant and susceptible linkers, digestion with Exo III, denaturing nucleic acids, reannealing previously denatured nucleic acids, and repetition of any of the previous steps (please refer to the entire document particularly Figure 1; columns 26-41, 43-46, 52-53, 55-62).

12. Claims 7-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Barany et al. U.S. patent 6,027,889 (filed May 28, 1997).

Barany et al. (see entire document) teach various PCR and LDR methods to form an array (e.g. library) of nucleic acids (please refer to column 5, lines 39-50). Barany et al. teach methods including the steps of digesting genomic DNA with restriction endonucleases including Taq I (e.g. present claim 7 step (A); please refer to column 24, lines 21-54, column 40, lines 18-46, and Examples 1 and 6), adding adjustment or linker sequences and having both exonuclease resistant and susceptible sequences (e.g. present claim 7 step (B); please refer to column 26, lines 6-36, column 40, lines 18-46, and Table 11), digesting nucleic acids with Exo III (e.g. present claim 7 step (E); please refer to column 26, lines 6-36), denaturing and hybridizing various nucleic acids (e.g. present claim 7 step (F); please refer to column 32, lines 34-42 and Examples 4 and 9-10). In addition, Barany et al. teach that the method steps can be repeated (e.g. present claim 7 steps (C)-(D); please refer to Examples 4, 6, and 9-10). Furthermore, Barany et al. teach contacting to optimize for a population (e.g. present claim 7 step (G); please refer to column 36, lines 23-37). Moreover, Barany et al. teach that Exo I can be utilized (e.g. present claims 8-9; please refer to column 26, lines 2-36). Therefore, one of skill in art would have anticipated the presently claimed invention in view of the teachings of Barany et al.

Arguments and Response

13. Applicant's arguments directed to the rejection under 35 USC 102(e) as being anticipated by Barany et al. for present claims 7-9 was considered but are not persuasive for the following reasons.

Applicant contends that every element of the claimed invention must be identically shown in a single reference and the Barany et al. patent does not teach the method embodied by steps (a)-(g) of the applicant's claim (cites MPEP § 2131 and *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990)). In addition, applicant contends that the specific term "library" does not appear in the Barany et al. reference.

Applicant's arguments are not convincing since the teachings of Barany et al. do anticipate the presently claimed method of the instant claims. It is the examiner's position that Barany et al. teaches each and every limitation of the presently claimed method (please refer to the rejection above). In addition, it is unclear what limitation(s) the applicant contends is missing from the Barany et al. reference since the applicant has failed to specifically point out the supposed shortcomings of Barany et al. It is the examiner's position that Barany et al. teaches methods comprising digesting nucleic acids with restriction enzymes, ligating linkers including Exo III resistant and susceptible linkers, digestion with Exo III, denaturing nucleic acids, reannealing previously denatured nucleic acids, and repetition of any of the previous steps (please refer to the entire document particularly Figures 1-24; columns 24-36; Examples 1-10). Regarding the specific term "library" in the preamble of the present claim, applicants are directed to MPEP § 2111.02. The term "library" does not provide additional structural information to the end product of the method. In addition, it is the examiner's position that the specific term "array" is a "library", collection, population, etc. organized in a specific arrangement. However, the rejection has been modified in order to clarify the interpretation of the term.

Claim Rejections - 35 USC § 103

14. Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. U.S. Patent 6,352,842 B1 (filed March 26, 1999) and Strathmann U.S. Patent 6,480,791 B1 (filed October 26, 1999).

Short et al. (see entire document) teach directed evolution utilizing restriction endonucleases and exonulcease III (please refer to the abstract). Short et al. teach methods of directed evolution including steps for digesting nucleic acids with various restriction enzymes or polynucleotide-acting enzymes (e.g. present claim 7; please refer to column 56, lines 23-67, columns 57-58, and column 59, lines 1-6), steps for producing Exo III resistant and susceptible nucleic acids or linkers (e.g. present claim 7; please refer to column 38, lines 24-67), steps for digesting nucleic acids with Exo III (e.g. present claim 7; please refer to column 37, lines 9-67, column 38, and column 39, lines 1-35), and steps for denaturing and hybridizing nucleic acids (e.g. present claim 7; please refer to column 37, lines 10-22 and 55-67, and column 38, lines 1-7). In addition, Short et al. teaches that the products of the directed evolution methods can be bound and enriched for members of the nucleic acid population which hybridize or bind (e.g. present claim 7; please refer to column 40, lines 38-60). Furthermore, Short et al. states that any commercially available or non-commercially available polynucleotide endonucleases can be utilized in the directed evolution methods including the presently elected species of Sau3A I and Taq I as evidenced by Roberts and Macelis (please refer to column 56, lines 42-57 and Roberts and Macelis, REBASE – restriction enzymes and methylases, Nucleic Acids Research, 24(1): 223-235, 1996).

However, Short et al. does not teach Exo I or biotin attached to a linker.

Strathmann (see entire document) teaches various methods of nucleic acid amplification and sequencing (please refer to the Summary columns 3-4). Strathmann teaches the use of various single strand dependent nucleases including S1 nuclease and mung bean nuclease (e.g. present claim 8, please refer to column 27, lines 21-53). In addition, Strathmann teaches the use of the single-strand dependent nuclease Exo I (e.g. present claim 9; please refer to column 15, lines 20-36). Furthermore, Strathmann teaches the attachment of biotin to various nucleic acid tags (e.g. present claim 10; please refer to column 13, lines 1-14).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the methods of directed evolution taught by Short et al. with the Exo I and biotin taught by Strathmann.

One having ordinary skill in the art would have been motivated to do this because both Short et al. and Strathmann teach methods which include PCR (please refer to Methodology section columns 28-34 of Short et al. and columns 13-15 of Strathmann). In addition, Strathmann teaches that tags including biotin are utilized to distinguish different sample polynucleotides in order to identify the polynucleotides (please refer to column 4, lines 38-67, column 5, lines 1-31, column 13, lines 1-5, column 27, lines 5-20, and column 30, lines 35-47). Furthermore, Strathmann teaches that the use of Exo I or other single-strand dependent nucleases is important for enhanced PCR amplification or to destroy mismatched duplexes and single-strand DNA (e.g. DNA without a complementary strand hybridized; please refer to column 15, lines 20-36 and column 27, lines 21-53).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the methods of directed evolution taught by Short et al. with the Exo I and biotin

taught by Strathmann because of the examples provided by Strathmann (please refer to Examples 1-4) and Short et al. (please refer to Examples 1-7).

Therefore, the modification of the methods of directed evolution taught by Short et al. with the Exo I and biotin taught by Strathmann render the instant claims prima facie obvious.

Arguments and Response

11. Applicant's arguments directed to the rejection under 35 USC 103(a) as being unpatentable over Short et al. and Strathmann for present claims 7-10 was considered but are not persuasive for the following reasons.

Applicant contends the Short et al. and Strathmann patents do not teach the method embodied by steps (a)-(g) of the applicant's claims.

Applicant's arguments are not convincing since the teachings of Short et al. and Strathmann do render obvious the presently claimed method of the instant claims. It is the examiner's position that Short et al. and Strathmann teaches each and every limitation of the presently claimed method. In addition, it is unclear what limitation(s) the applicant contends is missing from the Short et al. and Strathmann references since the applicant has failed to specifically point out the supposed shortcomings of Short et al. or Strathmann. It is the examiner's position that Short et al. teaches methods comprising digesting nucleic acids with restriction enzymes, ligating linkers including Exo III resistant and susceptible linkers, digestion with Exo III, denaturing nucleic acids, reannealing previously denatured nucleic acids, and repetition of any of the previous steps (please refer to the entire document particularly Figure 1; columns 26-41, 43-46, 52-53, 55-62) and Strathmann teaches biotin and single-strand dependent Exo I (please refer to entire document particularly columns 3-4, 13, 15, and 27).

26. Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. U.S. patent 6,027,889 (filed May 28, 1997) and Barany et al. U.S. Patent 6,534,293 B1 (filed January 5, 2000).

Barany et al. (6,027,889; see entire document) teach various PCR and LDR methods to form an array (e.g. library) of nucleic acids (please refer to column 5, lines 39-50). Barany et al. teach methods including the steps of digesting genomic DNA with restriction endonucleases including Taq I (e.g. present claim 7; please refer to column 24, lines 21-54, column 40, lines 18-46, and Examples 1 and 6), adding adjustment or linker sequences and having both exonuclease resistant and susceptible sequences (e.g. present claim 7; please refer to column 26, lines 6-36, column 40, lines 18-46, and Table 11), digesting nucleic acids with Exo III (e.g. present claim 7; please refer to column 26, lines 6-36), denaturing and hybridizing various nucleic acids (e.g. present claim 7; please refer to column 32, lines 34-42 and Examples 4 and 9-10). In addition, Barany et al. teach that the method steps can be repeated (e.g. present claim 7; please refer to Examples 4, 6, and 9-10). Furthermore, Barany et al. teach that Exo I can be utilized (e.g. present claims 8-9; please refer to column 26, lines 2-36).

Barany et al. (6,027,889) does not teach biotin attached to a linker.

Barany et al. (6,534,293; see entire document) teach methods for assembling genomic maps of an organism's DNA (please refer to the abstract). Barany et al. teach methods including the steps of cleaving DNA with restriction endonucleases including Taq I and adding linkers or adapters (please refer to column 11, lines 42-67, column 23, lines 7-18, column 28, lines 62-67,

column 29, lines 1-20). In addition, Barany et al. teaches that the linkers can also have biotin tags (e.g. present claim 10; please refer to Tables 8-9 and 13).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the PCR and LDR methods of Barany et al. (6,027,889) with the biotin tag of Barany et al. (6,534,293).

One having ordinary skill in the art would have been motivated to do this because Barany et al. (6,534,293) teach improved PCR and LDR methods to save time and money (please refer to column 11, lines 34-39). Furthermore, Barany et al. teach that biotin labels can be utilized to minimize false positives during the PCR and LDR methods and to purify specific sequences (please refer to column 66, lines 60-67 and columns 67-68).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the PCR and LDR methods of Barany et al. (6,027,889) with the biotin tag of Barany et al. (6,534,293) because of the various examples provided by Barany et al. (please refer to Examples 1-10 of 6,027,889 and Examples 1-6 of 6,534,293).

Therefore, the modification of the PCR and LDR methods of Barany et al. (6,027,889) with the biotin tag of Barany et al. (6,534,293) render the instant claims prima facie obvious.

Arguments and Response

13. Applicant's arguments directed to the rejection under 35 USC 103(a) as being unpatentable over Barany et al. and Barany et al. for present claims 7-10 was considered but are not persuasive for the following reasons.

Applicant contends that the Barany et al. and Barany et al. patents do not teach the method embodied by steps (a)-(g) of the applicant's claims.

Applicant's arguments are not convincing since the teachings of Barany et al. and Barany et al. do render obvious the claimed method of the instant claims. It is the examiner's position that Barany et al. and Barany et al. teach each and every limitation of the presently claimed method. In addition, it is unclear what limitation(s) the applicant contends is missing from the Barany et al. references since the applicant has failed to specifically point out the supposed shortcomings of the Barany et al. references. It is the examiner's position that Barany et al. teaches methods comprising digesting nucleic acids with restriction enzymes, ligating linkers including Exo III resistant and susceptible linkers, digestion with Exo III, denaturing nucleic acids, reannealing previously denatured nucleic acids, and repetition of any of the previous steps (please refer to the entire document particularly Figures 1-24; columns 24-36; Examples 1-10) and Barany et al. teaches biotin (please refer to entire document particularly columns 11, 23, 28, 29; Tables 8-9 and 13).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ADS
October 11, 2006

MARK SHIBUYA, PH.D.
PATENT EXAMINER